PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P016626WO ZCW	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2005/000605	International filing date *(day/month/year)* 21.02.2005	Priority date *(day/month/year)* 20.02.2004
International Patent Classification (IPC) or national classification and IPC INV. C07C233/68 C07C233/77 C07C63/04 C07C69/78 A61K31/167 A61K31/192 A61K31/216 A61K31/235		
Applicant UCL BIOMEDICA Plc et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 15 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 18 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.12.2005	07.07.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lorenzo Varela, M.J. Telephone No. +49 89 2399-8239

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000605

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-3, 6, 8-12, 15-21, 23-28, 31-62	as originally filed
4, 5, 5a, 7, 13, 14, 22, 29, 30, 63, [redacted]	filed with telefax on 20.12.2005

Claims, Numbers

1-40	filed with telefax on 20.12.2005

Drawings, Sheets

1/3-3/3	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☒ the description, pages 4,5,5a,7,13,14,22,29,30,63,64
   ☒ the claims, Nos. 1-40
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000605

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 37-41

because:

☒ the said international application, or the said claims Nos. 37-41 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000605

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9,17-40, 41, 43,44
	No:	Claims	1-8,10-16,42
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-44
Industrial applicability (IA)	Yes:	Claims	1-44
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

This report is based in the application as originally filed. The reason therefore is that the amendments submitted by fax on 20.12.05 do not fulfil the requirements of Rules 19(2) and 34(2) b) PCT; the amendments in the proviso in claim 1 under (i) and (ii) have no basis in the application as filed and as this proviso does not only exclude specific compounds disclosed in documents which do not relate to the same activity as the present application but it is more general; such amendments go beyond the disclosure of the application as filed and are not allowed under Rules 19(2) and 34(2) PCT. Hence, this international preliminary report is based on the description and claims as originally filed.

It is noted that the objections on paragraphs 40, 41, 43 and 44 would have been overcome with the amendments on pages 7, 22, 29, 30, 63 and 64 in the description.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 37-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OHSHIMA, ETSUO ET AL: "Synthesis and antiallergic activity of 11-(aminoalkylidene)-6,11- dihydrodibenz[b,e]oxepin derivatives" XP002333556 retrieved from STN Database accession no. 1992:255459

D2: WO 2004/078180 A2 (GUILFORD PHARMACEUTICALS INC., USA) 16 September 2004 (2004-09-16)

D3: WO 2004/074224 A1 (ASTRAZENECA AB, SWED.) 2 September 2004 (2004-09-

02)

D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ISHIKAWA, TADAHIRO ET AL: "Insulation film materials, varnishes containing them, polyoxazole-based microporous films with low moisture absorption manufactured from them, and semiconductor devices using them" XP002333557 retrieved from STN Database accession no. 2004:19987

D5: WO 03/106420 A1 (ASTRAZENECA A.B., SWED.) 24 December 2003 (2003-12-24)

D6: WO 03/091204 A1 (GLAXO GROUP LIMITED, UK) 6 November 2003 (2003-11-06)

D7: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OREN, JAKOB ET AL: "Photochemical studies. Part 31. Homoconjugated ketones with extended unsaturation: wavelength-selective, regioselective, diastereoselective, and enantiospecific photochemical transformations of methyl 7-oxospiro[5.5]undeca-1,3- and -2,4-diene-2-carboxylate" XP002333558 retrieved from STN Database accession no. 1993:580433

D8: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BERGMAN, NILS AAKE ET AL: "Chemical stability of a prostacyclin analog due to the absence of intramolecular catalysis" XP002333559 retrieved from STN Database accession no. 1988:221428

D9: DATABASE BEILSTEIN [Online] XP002333560 accession no. BRN 7478893

D10: DATABASE BEILSTEIN [Online] XP002333561 accession no. BRN 7705788

D11: DATABASE BEILSTEIN [Online] XP002333562 accession no. BRN 7704940

D12: DATABASE BEILSTEIN [Online] XP002333563 accession no. BRN 7434441

D13: DATABASE BEILSTEIN [Online] XP002333564 accession no. BRN 3414970

D14: DATABASE BEILSTEIN [Online] XP002333565 accession no. BRN 2803986

D15: DATABASE BEILSTEIN [Online] XP002333566 accession no. BRN 7478893

D16: DATABASE BEILSTEIN [Online] XP002333567 accession no. BRN 2576796

D17: DATABASE BEILSTEIN [Online] XP002333568 accession no. BRN 2093695

D18: DATABASE BEILSTEIN [Online] XP002333569 accession no. BRN 4862361

D19: DATABASE BEILSTEIN [Online] XP002333570 accession no. BRN 2720943

D20: DATABASE BEILSTEIN [Online] XP002333571 accession no. BRN 2578485

D21: DATABASE BEILSTEIN [Online] XP002333572 accession no. BRN 9028430

D22: DATABASE BEILSTEIN [Online] XP002333573 accession no. BRN 8102389

D23: DATABASE BEILSTEIN [Online] XP002333574 accession no. BRN 7884890
D24: DATABASE BEILSTEIN [Online] XP002333575 accession no. BRN 7884829
D25: DATABASE BEILSTEIN [Online] XP002333576 accession no. BRN 7595800
D26: DATABASE BEILSTEIN [Online] XP002333577 accession no. BRN 7157925
D27: DATABASE BEILSTEIN [Online] XP002333578 accession no. BRN 5989239
D28: DATABASE BEILSTEIN [Online] XP002333579 accession no. BRN 4000587
D29: DATABASE BEILSTEIN [Online] XP002333580 accession no. BRN 945016
D30: DATABASE BEILSTEIN [Online] XP002333583 accession no. BRN 433087
D31: DATABASE BEILSTEIN [Online] XP002333584 accession no. BRN 2381895
D32: WO0016756
D33: US5342971
D34: US2003/0191069

1. The present application relates to compounds according to formulae (I), (Ia), (Ib); their use in the preparation of medicaments for the treatment of muscular disorders/gastrointestinal disorders/the modulation of peripheral cannabinoid receptors; pharmaceutical compositions comprising them and their use in an assay for identifying modulators of cannabinoid receptor activity.

2. D1 discloses compound with rn:140439-65-2 which is novelty destroying for the subject-mater of claims 1, 3, 6-8, 11, 13-15 and 42.

3. D2 discloses compounds with rn:377731-28-7; 378242-26-3; 378242-27-4; 378242-49-0; 378242-61-6; 378242-62-7; 378242-63-8; 378242-66-1; 378243-04-0; 378243-05-1; 378243-06-2; 378243-07-3; 378243-08-4; 378243-14-2;378243-15-3; 378243-16-4; 378243-17-5; 378243-18-6; 378243-19-7; 378243-20-0; 378243-21-1; 378243-22-2; 378243-24-4; 378243-25-5; 378243-26-6; 378243-28-8; 378243-29-9; 378243-30-2 378243-32-4; 378243-67-5; 378243-68-6; 378243-72-2; 378243-77-7; 378243-80-2; 378243-81-3; 475653-40-8; 378242-22-9 according to claims 1-6, 11, 13-16 and 42.

4. D3 discloses compounds with rn: 749229-45-6; 749229-46-7; 749229-47-8; 749229-48-9; 749229-74-1; 749229-75-2; 749229-76-3; 749223-15-6; 749229-61-6; 749229-62-7; 749229-63-8; 749229-64-9 according to claims 1-6, 11, 13-16 and 42.

5. D4 discloses compound with rn:393543-03-8. This disclosure anticipates the subject-matter of claims 1-8, 11, 13-16 and 42.

6. D5 discloses compounds with rn:637300-47-1; 637300-70-0; 637300-71-1; 637300-74-4; 637300-75-5; 637300-76-6; 637300-77-7; 637300-78-8; 637300-79-9; 637300-80-2; 637300-81-3; 637300-82-4; 637300-85-7; 637300-90-4; 637301-08-7; 637300-99-3; 637301-00-9. This disclosure anticipates the subject-matter of claims 1-6,11, 13-16 and 42.

7. D6 discloses compounds with rn:620601-11-8; 620601-12-9; 620601-13-0; 620601-15-2; 620601-16-3; 620601-20-9; 620599-79-3; 620599-80-6; 620599-83-9; 620599-84-0. This disclosure anticipates the subject-matter of claims 1-8, 10, 11, 13-16 and 42.

8. D7 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1, 6, 7, 11, 13, 14 and 42.

9. D8 discloses compounds falling under formula (I) which anticipate the subject-mater of claims 1-9, 11, 13-16 and 42.

10. D9 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11, 14-16 and 42.

11. D10 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 8, 11, 13-16 and 42.

12. D11 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1, 7, 11, 13, 15 and 42.

13. D12 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1,-5, 7, 11, 13, 14 and 42.

14. D13 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11, 13, 14 and 42.

15. D14 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11 and 42.

16. D15 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11, 15, 16 and 42.

17. D16 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11 and 42.

18. D17 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 11 and 42.

19. D18 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 11, 12, 14-16 and 42.

20. D19 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1, 3, 11, 12, 14, 15 and 42.

21. D20 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 11, 12, 14 and 42.

22. D21 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-4, 6, 11 and 42.

23. D22 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42.

24. D23 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42.

25. D24 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42.

26. D25 discloses a compound falling under formula (I) which anticipates the subject-mater

of claims 1-6, 13 and 42.

27. D26 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13, 14 and 42.

28. D27 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42.

29. D28 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42.

30. D29 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 12 and 42.

31. D30 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11 and 42.

32. D31 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-7, 11, 12, 14-16 and 42.

33. D32- D34 disclose cannabinoid receptors comprising an aromatic moiety attached to a carboxylic or to an amide moiety and to a polar functional group.

Novelty

34. The subject-matter of claims 1-8, 10-16 and 42 is not novel in the sense of Art. 33(2) PCT.

a. D1 discloses compound with rn:140439-65-2 which is novelty destroying for the subject-mater of claims 1, 3, 6-8, 11, 13-15 and 42.

b. D4 discloses compound with rn:393543-03-8. This disclosure anticipates the subject-matter of claims 1-8, 11, 13-16 and 42, which is therefore not novel.

c. D5 discloses compounds with rn:637300-47-1; 637300-70-0; 637300-71-1; 637300-74-4; 637300-75-5; 637300-76-6; 637300-77-7; 637300-78-8; 637300-79-9; 637300-80-2; 637300-81-3; 637300-82-4; 637300-85-7; 637300-90-4; 637301-08-7; 637300-99-3; 637301-00-9. This disclosure anticipates the subject-matter of claims 1-6,11, 13-16 and 42, which is therefore not novel.

d. D6 discloses compounds with rn:620601-11-8; 620601-12-9; 620601-13-0; 620601-15-2; 620601-16-3; 620601-20-9; 620599-79-3; 620599-80-6; 620599-83-9; 620599-84-0. This disclosure anticipates the subject-matter of claims 1-8, 10, 11, 13-16 and 42, which is therefore not novel.

e. D7 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1, 6, 7, 11, 13, 14 and 42, which is therefore not novel.

f. D8 discloses compounds falling under formula (I) which anticipate the subject-mater of claims 1-9, 11, 13-16 and 42, which is therefore not novel.

g. D9 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11, 14-16 and 42, which is therefore not novel.

h. D10 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 8, 11, 13-16 and 42, which is therefore not novel.

i. D11 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1, 7, 11, 13, 15 and 42, which is therefore not novel.

j. D12 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1,-5, 7, 11, 13, 14 and 42, which is therefore not novel.

k. D13 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11, 13, 14 and 42, which is therefore not novel.

l. D14 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11 and 42, which is therefore not novel.

m. D15 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11, 15, 16 and 42, which is therefore not novel.

n. D16 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 7, 11 and 42, which is therefore not novel.

o. D17 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 11 and 42, which is therefore not novel.

p. D18 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 11, 12, 14-16 and 42, which is therefore not novel.

q. D19 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1, 3, 11, 12, 14, 15 and 42, which is therefore not novel.

r. D20 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-5, 11, 12, 14 and 42, which is therefore not novel.

s. D21 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-4, 6, 11 and 42, which is therefore not novel.

t. D22 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42, which is therefore not novel.

u. D23 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42, which is therefore not novel.

v. D24 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42, which is therefore not novel.

w. D25 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 13 and 42, which is therefore not novel.

x. D26 discloses a compound falling under formula (I) which anticipates the subject-mater

of claims 1-6, 11, 13, 14 and 42, which is therefore not novel.

y. D27 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42, which is therefore not novel.

z. D28 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11, 13 and 42, which is therefore not novel.

a'. D29 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 12 and 42, which is therefore not novel.

b'. D30 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-6, 11 and 42, which is therefore not novel.

c'. D31 discloses a compound falling under formula (I) which anticipates the subject-mater of claims 1-7, 11, 12, 14-16 and 42, which is therefore not novel.

Inventive step

35. The subject-matter of claims 9, 17-41, 43 and 44 does not involve an inventive step in the sense of Art. 33(3) PCT.

a. Modulators of cannabinoid receptors with a structure comprising an aromatic ring attached to a carboxylic or amide moiety and with another polar moiety in the structure are known in the art (D32-D34).

b. The provision of further compounds with the same technical features in the structure and with the same activity would be obvious for the skilled person in the art. Furthermore, activity data has only been provided for one single compound, compound 16. Inventive step could only be acknowledged if activity data are provided for a broader scope of compounds and the scope of the protection is restricted to compounds covered by the technical features in the formula of the tested compounds provided showing an unexpected effect such as improved aqueous solubility and/or decreased lipophilicity (as reported on page 5 of the description) over known cannabinoid receptor modulators

(comparative examples). As such an evidence of improvement over the prior art and activity data which covers a reasonable scope of the protection are not available at the moment, inventive step cannot be acknowledged.

Further comments

36. Documents D2 and D3 could become very relevant to assess the patentability of the present application when it enters the national/regional phase. No check has been carried out whether the priority dates of the present application and D2 and D3 have been validly claimed.

37. For the assessment of the present claims 37-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

38. The same formula is named (I) in claim 1 but (Ia) in claims 20, 22 and 23, leading therefore to lack of clarity, contrary to Art. 6 PCT.

39. There is a typing mistake in claim 9.

40. The expression "the contents of which are incorporated herein by reference" used in the description renders unclear the scope of the protection sought, contrary to Art. 6 PCT.

41. The use of the terms "and the like" in the description renders unclear the scope of the protection sought, contrary to Art. 6 PCT.

42. The use of the word "approximately" in the description renders unclear the scope of the protection sought, contrary to Art. 6 PCT.

43. The passages on page 29 from line 24 to 32 renders unclear the scope of the protection

sought, contrary to Art. 6 PCT. The skilled person in the art would not know which specific compounds fall within the scope of the protection, contrary to Art. 6 PCT. These passages should not have been included in the description.

44. The last paragraph in the description is vague and ambiguous rendering therefore unclear the scope of the protection sought, contrary to Art. 6 PCT.

45. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D32-D34 is not mentioned in the description, nor are these documents identified therein.

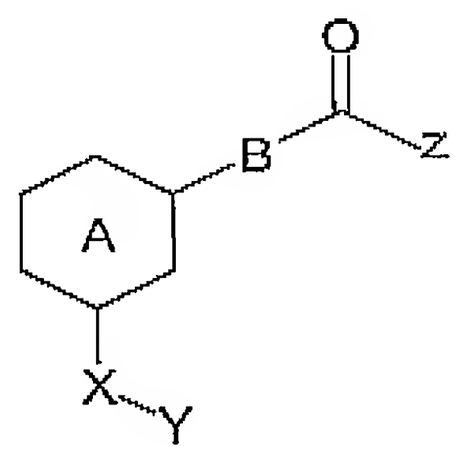
passive diffusion across plasma membranes or by active transport mechanisms. The BBB thus forms an effective barrier to many peripherally circulating substances.

An alternative method of excluding compounds from the brain is to incorporate structural features which enable them to be actively pumped across the BBB. One such example is the opioid agonist loperamide; although lipophilic, loperamide contains structural features recognized by the p-glycoprotein transporter (MDR1) that allow it to be actively pumped across the blood brain barrier. [Wandel, C. *et al*, *Anesthesiology* 2002, *96*, 913-920; Seelig, A. *et al*, *Eur. J. Pharm. Sci.* 2000, *12*, 31-40].

The present invention seeks to provide new cannabinoid receptor modulators. More particularly, the invention seeks to provide cannabinoid receptor modulators that alleviate and/or eliminate some of the disadvantages commonly associated with prior art modulators, for example undesirable psychoactive side effects. More specifically, though not exclusively, the invention seeks to provide modulators that selectively target peripheral cannabinoid receptors.

STATEMENT OF INVENTION

A first aspect of the invention relates to a compound of formula I, or a pharmaceutically acceptable salt thereof,



wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted by one or more substituents selected from alkyl, COOH, CO_2-alkyl, alkenyl, CN, NH_2, hydroxy, halo, alkoxy, CF_3 and nitro;

Y is a polar functional group selected from OH, NO_2, CN, COR^3, $COOR^3$, NR^3R^4, $CONR^3R^4$, SO_3H, SO_2-R^3, $SO_2NR^3R^4$ and CF_3, where each of R^3 and R^4 is independently H or a hydrocarbyl group;

A is phenyl or pyridyl; and

B is $(CH_2)_n$ where n is 0;

with the proviso that:

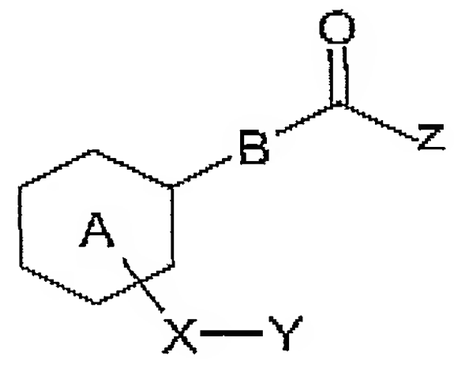
(i) when A is phenyl, and Z is OH, X-Y is other than C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2CO_2Me$, $(CH_2)_4CO_2H$; and

(ii) when A is phenyl, and Z is OMe, X-Y is other than C≡C-$(CH_2)_4$OH; -$(CH_2)_4$-CHO, *cis*-CH=CH-$(CH_2)_3$OH, *trans*-CH=CH-$(CH_2)_3$OH;

and wherein the compound is other than 1-(N-octylcarbamoyl)methyl-3-carboxamidopyridinuim chloride, 3-methylcarbamoyl-1-dodecyloxycarbonylmethyl-pyridinium or 6-aminomethylpyridine-2-carboxylic acid ethyl ester.

Advantageously, the compounds of the present invention preferably exhibit improved aqueous solubility and/or decreased lipophilicity compared to prior art cannabinoid receptor modulators.

A second aspect of the invention relates to the use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

acid. Other examples of cannabinoids include anandamide, methanandamide and R(+)WIN55,212.

ENDOCANNABINOID

This term means a cannabinoid that exists naturally in the body – as opposed to an exogeneously supplied cannabinoid. Endocannabinoids are discussed by Di Marzo (1998) Biochimica et Biophysica Acta vol 1392 pages 153-175. An example of an endocannabinoid is anandamide. Teachings on this entity and anandamide amidase may be found in US-A-5874459. This document teaches the use of anandamide amidase inhibitors as analgesic agents.

CANNABINOID RECEPTOR

A cannabinoid receptor is any one or more of several membrane proteins that bind cannabinol and structurally similar compounds and mediate their intracellular action.

Two receptors for the psychoactive ingredient of marijuana Δ^9–tetrahydrocannabinol (THC), the CB1 and CB2 cannabinoid receptors, have been found (Pertwee 1997 Pharmacol Ther vol 74 129-180). Both of these receptors are seven-transmembrane-domain G-protein-coupled receptors. CB_1 receptors are found in the brain and testis. CB_2 receptors are found in the spleen and not in the brain.

For both types of receptor arachidonoylethanolamide (anandamide) is a putative endogenous ligand and both types are negatively coupled to adenylate cyclase decreasing intracellular cyclic AMP levels. Examples of sequences for such receptors are from *Mus musculus* – and include: CB1, database code CB1R_MOUSE, 473 amino acids (52.94 kDA); CB2, database code CB2R_MOUSE, 347 amino acids (38.21 kDa). More details on CB1 and CB2 now follow.

CANNABINOID RECEPTOR 1 (CB_1 or CNR1)

Background teachings on CB_1 have been presented by Victor A. McKusick *et al* on http://www.ncbi.nlm.nih.gov/Omim. The following information concerning CB_1 has

independently H or an alkyl group optionally substituted by one or more substituents selected from hydroxy, halo-, alkoxy-, nitro-, and a cyclic group.

For compounds of formula I, more preferably still, Y is selected from OH, CN, COOMe, COOH, $CONH_2$, CONHMe and $CONMe_2$.

For all the above embodiments, preferably each of R^1, R^2, R^3 and R^4 is independently H, an alkyl group, an aryl group, or a cycloalkyl group, each of which may be optionally substituted by one or more substituents selected from hydroxy, halo-, alkoxy-, nitro-, and a cyclic group.

In one particularly preferred embodiment of the invention for compounds of formula Ia, n is 0; i.e., B is absent and the -C(=O)Z moiety is attached directly to aryl group, A.

For compounds of formula I and Ia, preferably, X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$;

$-C(R^5)=C(R^6)-(CH_2)_q-Y$; and

$-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-Y$;

where each of R^5, R^6, R^7 and R^8 is independently H or alkyl, and each of p, q and r is independently 1 to 6, more preferably, 2, 3, or 4.

For compounds of formula I and Ia, even more preferably, X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$; and

$-CH=CH-(CH_2)_q-Y$;

where each of p and q is independently 1 to 6, more preferably 2, 3, or 4.

In one preferred embodiment, R^5 and R^6 are both H.

For compounds of formula I and Ia, in one especially preferred embodiment, X-Y is

cis $-C(R^5)=C(R^6)-(CH_2)_q-Y$

For compounds of formula I and Ia, in another preferred embodiment, X-Y is

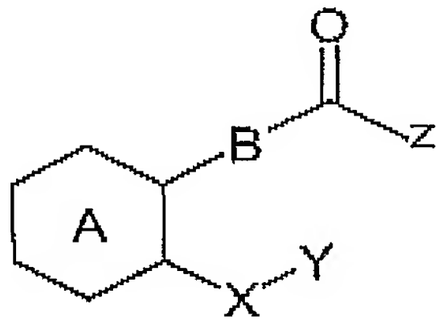
$-C(Me)_2-CH_2-(CH_2)_r-Y$ and r is 1 to 6, more preferably, 2, 3 or 4.

In another preferred embodiment, X-Y is $(CH_2)_s$-Y where s is 1 to 6, more preferably, 2, 3, 4 or 5.

Preferably, for compounds of formula Ia, A is an optionally substituted phenyl or pyridyl group, more preferably a phenyl group.

In another preferred embodiment, A is an unsubstituted phenyl or pyridyl group, more preferably an unsubstituted phenyl group.

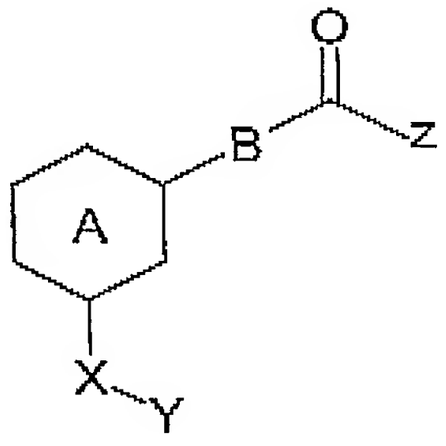
For compounds of formula Ia, in one particularly preferred embodiment, the compound is of formula Ib



Ib

wherein A, B, X, Y and Z are as defined above.

For compounds of formula Ia, in another particularly preferred embodiment, the compound is of formula Ic



Ic

wherein A, B, X, Y and Z are as defined above.

Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985).

Examples of suitable carriers include lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol and sorbitol. Examples of suitable diluents include ethanol, glycerol and water.

The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, or in addition to, the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

Examples of suitable binders include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol.

Examples of suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate and sodium chloride.

Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

SALTS/ESTERS

The compounds of the invention can be present as salts or esters, in particular pharmaceutically acceptable salts or esters.

One aspect of the invention relates to a process comprising the steps of:

(a) performing an assay method described hereinabove;

(b) identifying one or more candidate compounds capable of modulating one or more cannabinoid receptors; and

(c) preparing a quantity of said one or more candidate compounds.

Another aspect of the invention provides a process comprising the steps of:

(a) performing an assay method described hereinabove;

(b) identifying one or more candidate compounds capable of modulating one or more cannabinoid receptors;

(c) preparing a pharmaceutical composition comprising said one or more candidate compounds.

Another aspect of the invention provides a process comprising the steps of:

(a) performing an assay method described hereinabove;

(b) identifying one or more candidate compounds capable of modulating one or more cannabinoid receptors;

(c) modifying said one or more candidate compounds capable of modulating one or more cannabinoid receptors;

(d) performing the assay method described hereinabove;

(e) optionally preparing a pharmaceutical composition comprising said one or more candidate compounds.

The above methods may be used to screen for a candidate compound useful as an modulators of one or more cannabinoid receptors, more preferably peripheral cannabinoid receptors.

REPORTERS

A wide variety of reporters may be used in the assay methods (as well as screens) of the present invention with preferred reporters providing conveniently detectable signals (eg. by spectroscopy). By way of example, a reporter gene may encode an enzyme which catalyses a reaction which alters light absorption properties.

Other protocols include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescent activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilising monoclonal antibodies reactive to two non-interfering epitopes may even be used. These and other assays are described, among other places, in Hampton R et al [1990, Serological Methods, A Laboratory Manual, APS Press, St Paul MN] and Maddox DE et al [1983, J Exp Med 15 8:121 1].

Examples of reporter molecules include but are not limited to (galactosidase, invertase, green fluorescent protein, luciferase, chloramphenicol, acetyltransferase, (glucuronidase, exo-glucanase and glucoamylase. Alternatively, radiolabelled or fluorescent tag-labelled nucleotides can be incorporated into nascent transcripts which are then identified when bound to oligonucleotide probes.

By way of further examples, a number of companies such as Pharmacia Biotech (Piscataway, NJ), Promega (Madison, WI), and US Biochemical Corp (Cleveland, OH) supply commercial kits and protocols for assay procedures. Suitable reporter molecules or labels include those radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors and magnetic particles. Patents teaching the use of such labels include US-A-3817837; US-A-3850752; US-A-3939350; US-A-3996345; US-A-4277437; US-A-4275149 and US-A-4366241.

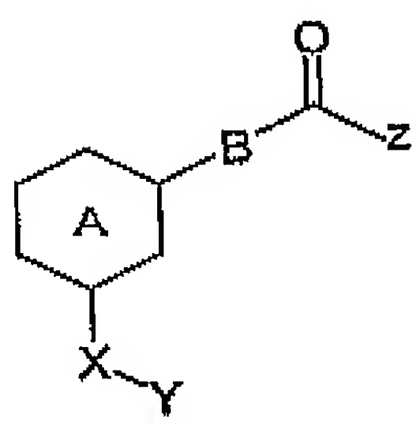
to hindlimb flexion using a strain gauge [Baker, D. *et al*, *Nature* 2000, *404*, 84-87]. Animals serve as their own controls and will be analysed in a pairwise fashion. To reduce the number of animals, effort and expense, following a drug–free period (spasticity returns within 24h) these animals receive different doses and or vehicle. Low doses of CB_1 agonists and CNS active CP55,940, as control, are locally (subcutaneous, intra-muscularly) administered into spastic ABH mice and the lack of activity in a contralateral limb analysed [Fox, A. *et al*, *Pain* 2001, *92*, 91-100]. Expression of CB_1 in the peripheral nervous system, including dorsal root ganglia, a non-CNS site for CB-mediated nociception can be removed using peripherin-Cre transgenic mouse [Zhou, L. *et al*, *FEBS Lett.* 2002, *523*, 68-72]. These conditional KO mice are maintained on the C57BL/6 background. These mice develop EAE following induction with myelin oligodendrocyte glycoprotein residues 35-55 peptide [Amor, S. *et al*, *J. Immunol.* 1994, *153*, 4349-4356].

<u>*In vivo* evaluation in normal and CREAE mice</u>

A CNS excluded compound provides a tool for examining if a component of a cannabinoid anti-spastic effect is mediated *via* peripheral CB receptors. Compound **(16)** was examined for CNS effects in normal mice as shown in Figures 2 and 3. At a dose of 1mg/kg no hypothermia or hypomotility was observed. In CREAE mice a marked effect on spasticity was noticed (Figure 4) providing strong evidence that a selective inhibition of spasticity is achievable without producing CNS effects. As stated above there is no established role for peripheral cannabinoid receptors in the control of spasticity, however, spasticity is likely to be a product of nerve damage in the spinal cord, at least in EAE, [Baker, D. *et al*, *FASEB J.* 2001, *15*, 300-302; Baker, D. *et al*, *J. Neuroimmunol.* 1990, *28*, 261-270] andaberrant signals to and from the musculature are likely, at least in part to contribute to the muscle spasms occuring in spasticity.

CLAIMS

1. A compound of formula I, or a pharmaceutically acceptable salt thereof,



wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted by one or more substituents selected from alkyl, COOH, CO_2-alkyl, alkenyl, CN, NH_2, hydroxy, halo, alkoxy, CF_3 and nitro;

Y is a polar functional group selected from OH, NO_2, CN, COR^3, $COOR^3$, NR^3R^4, $CONR^3R^4$, SO_3H, SO_2-R^3, $SO_2NR^3R^4$ and CF_3, where each of R^3 and R^4 is independently H or a hydrocarbyl group;

A is phenyl or pyridyl; and

B is $(CH_2)_n$ where n is 0;

with the proviso that:

(i) when A is phenyl, and Z is OH, X-Y is other than C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2$OH, C≡C-$(CH_2)_2CO_2Me$, $(CH_2)_4CO_2H$; and

(ii) when A is phenyl, and Z is OMe, X-Y is other than C≡C-$(CH_2)_4$OH; -$(CH_2)_4$-CHO, *cis*-CH=CH-$(CH_2)_3$OH, *trans*-CH=CH-$(CH_2)_3$OH;

and wherein the compound is other than 1-(N-octylcarbamoyl)methyl-3-carboxamidopyridinuim chloride, 3-methylcarbamoyl-1-dodecyloxycarbonylmethyl-pyridinium or 6-aminomethylpyridine-2-carboxylic acid ethyl ester.

2. A compound according to claim 1 wherein Y is selected from CN, OH, $COOR^3$, $SO_2NR^3R^4$, $CONR^3R^4$, where each of R^3 and R^4 is independently H or a hydrocarbyl group.

3. A compound according to any preceding claim wherein each of R^1,R^2, R^3 and R^4 is independently H, an alkyl group, an aryl group, or a cycloalkyl group, each of which may be optionally substituted.

4. A compound according to any preceding claim wherein Y is selected from OH, CN, $COOR^3$, $CONR^3R^4$, where each of R^3 and R^4 is independently H or an optionally substituted alkyl group.

5. A compound according to any preceding claim wherein Y is selected from OH, CN, COOMe, COOH, $CONH_2$, CONHMe and $CONMe_2$.

6. A compound according to any preceding claim wherein X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$;

$-C(R^5)=C(R^6)-(CH_2)_q-Y$; and

$-C(R^5)(R^6)C(R^7)(R^8)-(CH_2)_r-Y$;

wherein each of R^5, R^6, R7, and R^8 is independently H or alkyl, and each of p, q and r is independently 2, 3, or 4.

7. A compound according to any preceding claim wherein X-Y is selected from

$-C\equiv C-(CH_2)_p-Y$; and

$-CH=CH-(CH_2)_q-Y$;

wherein each of p and q is independently 2, 3 or 4.

8. A compound according to claim 6 wherein X-Y is

cis-$C(R^5)=C(R^6)-(CH_2)_q-Y$ and q is 2, 3 or 4.

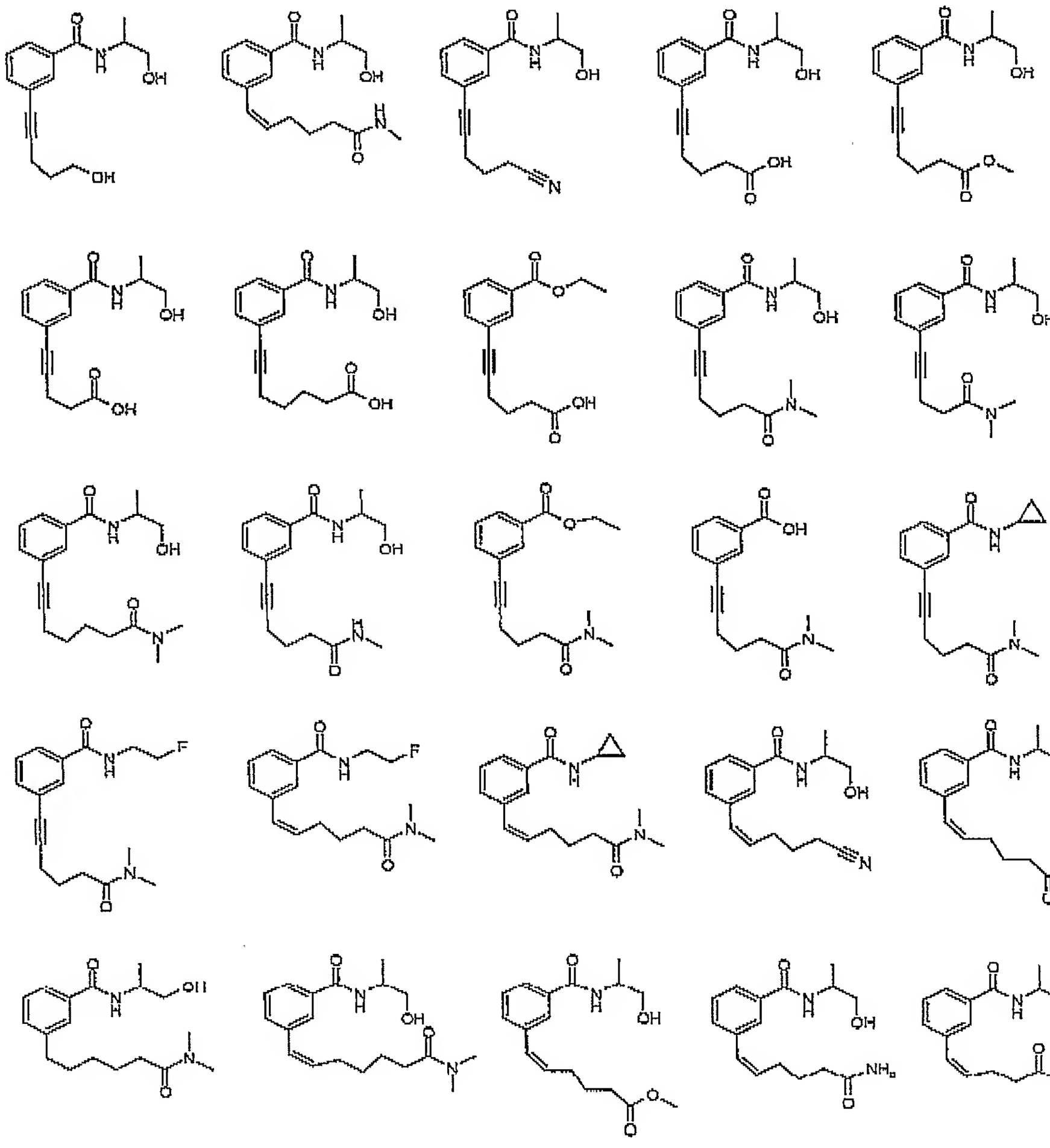
9. A compound according to any one of claims 1 to 6 or claim 8 wherein X-Y is $-C(Me)_2-CH_2-(CH_2)_r-Y$ and r is 2, 3 or 4.

10. A compound according to claim 1 wherein A is phenyl.

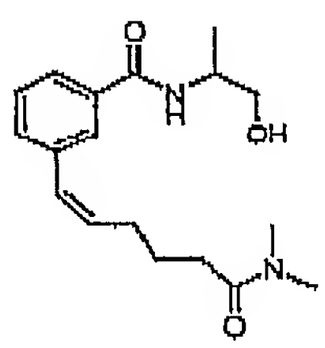
11. A compound according to any preceding claim wherein Z is OR^1 or NR^1R^2 and each of R^1 and R^2 is independently H, an alkyl or a cycloalkyl group, each of which may be optionally substituted by one or more OH or halogen groups.

12. A compound according to any preceding claim wherein Z is selected from OH, OEt, $NHCH_2CH_2F$, NH-cyclopropyl, $NHCH(Me)CH_2OH$ and $NHCH_2CH_2OH$.

13. A compound according to any preceding claim which is selected from the following:

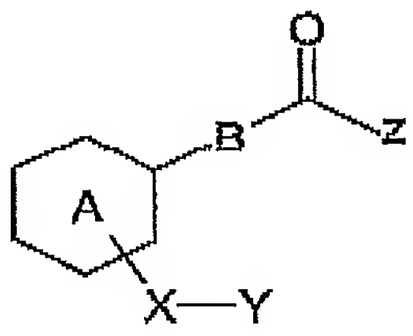


14. The compound of claim 13 which is



15. The compound of claim 14 which is in the form of a racemic mixture.

16. Use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted;

Y is a polar functional group;

A is an aryl or heteroaryl group, each of which may be optionally substituted; and

B is $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5;

in the preparation of a medicament for treating a muscular disorder.

17. Use according to claim 16 wherein the muscular disorder is a neuromuscular disorder.

18. Use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,

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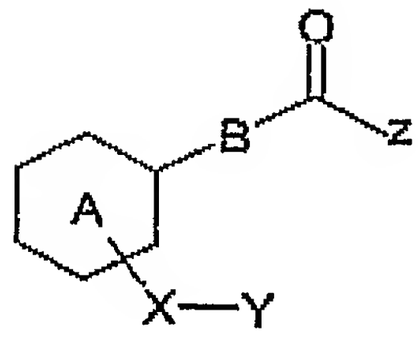


Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted;

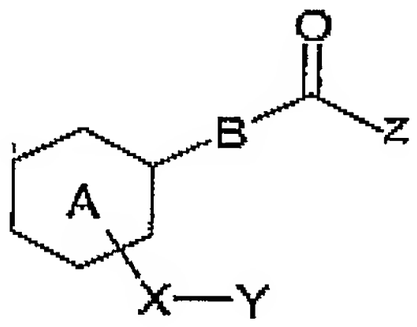
Y is a polar functional group;

A is an aryl or heteroaryl group, each of which may be optionally substituted; and

B is $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5;

in the preparation of a medicament for controlling spasticity and tremors.

19. Use of a compound of formula Ia, or a pharmaceutically acceptable salt thereof,



Ia

wherein

Z is OR^1 or NR^1R^2 wherein each of R^1 and R^2 is independently H, or a hydrocarbyl group;

X is an alkylene, alkenylene, or alkynylene group, each of which may be optionally substituted;

Y is a polar functional group;

A is an aryl or heteroaryl group, each of which may be optionally substituted; and

B is $(CH_2)_n$ where n is 0, 1, 2, 3, 4 or 5;

in the preparation of a medicament for treating a gastrointestinal disorder.

20. Use according to claim 19 wherein the gastrointestinal disorder is a gastric ulcer.

21. Use according to claim 19 wherein the gastrointestinal disorder is Crohn's disease.

22. Use according to claim 19 wherein the gastrointestinal disorder is secretory diarroehea.

23. Use according to claim 19 wherein the gastrointestinal disorder is paralytic ileus.

24. Use according to any one of claims 16 to 23 wherein said modulator selectively modulates peripheral cannabinoid receptors.

25. Use according to any one of claims 16 to 24 wherein said compound selectively modulates peripheral cannabinoid receptors over central cannabinoid receptors.

26. Use according to any one of claims 16 to 25 wherein the compound binds substantially exclusively to peripheral cannabinoid receptors.

27. Use according to any one of claims 16 to 26 wherein the compound is a cannabinoid receptor agonist.

28. Use according to any one of claims 16 to 27 wherein the compound does not substantially agonise central cannabinoid receptors.

29. Use according to any one of claims 16 to 28 wherein the compound is substantially excluded from the CNS.

30. Use according to any one of claims 16 to 29 wherein Y is selected from NO_2, CN, OR^3, COR^3, $COOR^3$, NR^3R^4, $CONR^3R^4$, SO_3H, SO_2-R^3, $SO_2NR^3R^4$ and CF_3, where each of R^3 and R^4 is independently H or a hydrocarbyl group.

31. Use compound according to any one of claims 16 to 30 wherein Y is selected from CN, $COOR^3$, $SO_2NR^3R^4$, $CONR^3R^4$, where each of R^3 and R^4 is independently H or a hydrocarbyl group.

32. Use according to any one of claims 16 to 31 wherein the compound is as defined in any one of claims 1 to 15.

33. A method of treating a disorder associated with the modulation of peripheral cannabinoid receptors, said method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 15.

34. A method according to claim 33 wherein said disorder is associated with peripheral cannabinoid receptor deactivation.

35 A method according to claim 33 or claim 34 wherein the compound does not substantially agonise central cannabinoid receptors.

36. A method according to any one of claims 33 to 35 wherein the compound binds substantially exclusively to peripheral cannabinoid receptors.

37. A method according to any one of claims 33 to 36 wherein the compound is subetantially excluded from the CNS.

38. A pharmaceutical composition comprising a compound according to any one of cla claims 1 to 15, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable diluent, excipient or carrier.

39. Use of a compound of formula Ia, or pharmaceutically acceptable salt thereof, as defined in claim 16 in an assay for identifying further compounds capable of modulating cannabinoid receptor activity.

40. Use according to claim 39 wherein the assay is a competitive binding assay.